PATENT COOPERATION TREATY

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INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 46562/276067	**FOR FURTHER ACTION**	See Form PCT/IPEA/416
International application No. PCT/US2004/008700	International filing date *(day/month/year)* 22.03.2004	Priority date *(day/month/year)* 21.03.2003

International Patent Classification (IPC) or national classification and IPC
A61K31/195, A61K31/216, A61K31/197

Applicant
DYNOGEN PHARMACEUTICALS, INC. et al.

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 8 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☒ *sent to the applicant and to the International Bureau)* a total of 6 sheets, as follows:
      ☒ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

☒	Box No. I	Basis of the opinion
☐	Box No. II	Priority
☒	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☐	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☒	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☐	Box No. VIII	Certain observations on the international application

Date of submission of the demand	Date of completion of this report
19.01.2005	29.07.2005

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INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/US2004/008700

Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This report is based on translations from the original language into the following language , which is the language of a translation furnished for the purposes of:
   - ☐ international search (under Rules 12.3 and 23.1(b))
   - ☐ publication of the international application (under Rule 12.4)
   - ☐ international preliminary examination (under Rules 55.2 and/or 55.3)

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

Description, Pages	
1-108	as originally filed
Claims, Numbers	
1-33	filed with telefax on 10.11.2004
Drawings, Sheets	
1/4-4/4	as originally filed

   ☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☒ The amendments have resulted in the cancellation of:
   - ☐ the description, pages
   - ☒ the claims, Nos. 34-38
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

* *If item 4 applies, some or all of these sheets may be marked "superseded."*

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
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Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 1-14 with respect to industrial applicability

because:

☒ the said international application, or the said claims Nos. 1-14 with respect to industrial applicability relate to the following subject matter which does not require an international preliminary examination (specify):

see separate sheet

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the said claims Nos.

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form	☐	has not been furnished
	☐	does not comply with the standard
the computer readable form	☐	has not been furnished
	☐	does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/US2004/008700

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-33
	No:	Claims	-
Inventive step (IS)	Yes:	Claims	-
	No:	Claims	1-33
Industrial applicability (IA)	Yes:	Claims	15-33
	No:	Claims	-

2. Citations and explanations (Rule 70.7):

see separate sheet

Box No. VI Certain documents cited

1. Certain published documents (Rule 70.10)

and / or

2. Non-written disclosures (Rule 70.9)

see separate sheet

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Claims 1-14 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. The following documents are referred to in this communication; the numbering will be adhered to in the rest of the procedure:

D1: JOURNAL OF PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS, vol. 303, no. 2, November 2002, pages 730-735.

D2: WO 01/24792 A (HUGHES JOHN ; SINGH LAKHBIR (GB); WARNER LAMBERT CO (US)) 12 April 2001.

D3: WO 01/01983 A (SINGH LAKHBIR ; WARNER LAMBERT CO (US); BRUMMEL ROGER N (US)) 11 January 2001.

D4: WO 03/000642 A (NICOX SA ; DEL SOLDATO PIERO (IT); ONGINI ENNIO (IT)) 3 January 2003.

D8: KATZUNG BG: "Basic & Clinical Pharmacology, Eighth edition" 2001, LANGE MEDICAL BOOKS/MCGRAW-HILL , UNITED STATES OF AMERICA.

D9: HOLMQUIST G L: "Drug decisions for patients with chronic noncancer pain syndromes" DRUG BENEFIT TRENDS 2001 UNITED STATES, vol. 13, no. 5, 2001, pages 36-38+41.

D10: WO 03/070237 A (TAYLOR CHARLES PRICE JR ; WARNER LAMBERT

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D11: WO 2004/054560 A (WESTBROOK SIMON LEMPRIERE ; TAYLOR CHARLES PRICE JR (US); WARNER LAMBE) 1 July 2004.

1.1 Unless indicated, reference is made to the passages indicated in the international search report.

1.2 The attention of the Applicant is drawn to the fact that the contents of D10 and D11 could become relevant for the questions of novelty and/or inventive step of the present claims during the European phase examination procedure.

2. **Novelty (Art. 33(2) PCT)**

None of the documents cited in the international search report discloses compositions or packaged kits comprising an $\alpha_2\delta$ subunit calcium channel modulator and a smooth muscle modulator selected from the group consisting of an antimuscarinic, a β3 adrenergic agonist and a bradykinin receptor antagonist. Therefore, the subject-matter of the present claims 1-33 is considered novel.

3. Inventive Step (Art. 33(3) PCT)

3.1 Present claims relate to pharmaceutical compositions and packaged kits comprising an $\alpha_2\delta$ subunit calcium channel modulator and a smooth muscle modulator selected from the group consisting of an antimuscarinic, a β3 adrenergic agonist and a bradykinin receptor antagonist, and their use for the treatment of pain.

3.2 D1 discloses that gabapentin and the neurokinin-1 receptor antagonist CI-1021 act synergistically in two rat models of neuropathic pain.

D2 shows that combinations of a NK1 receptor antagonist and a GABA analog such as gabapentin or pregabalin have synergistic effects in the treatment of pain.

D3 discloses synergistic combinations comprising gabapentin and pregabalin and their use in the treatment of pain. Gabapentin is also known to have spasmolytic properties (see D8, page 459, column 2, 3rd paragraph).

D4 concerns nitro-oxyderivative compounds for the treatment of neuropathic pain. The preferred precursor drugs of said nitro-oxyderivative compounds are gabapentin (also called NO-gabapentin therein) and pregabalin. Further, the combination of said derivatives of gabapentin and pregabalin with other NO-donors such as nitroglycerin is mentioned on page 18, paragraphs 3 to 6.

D9 mentions that gabapentin and oxybutynin are used for the treatment of chronic pain of neuropathic and nociceptive origin.

3.3 The problem to be solved by present application can be defined as to provide a composition for treating pain. The solution provided by the application is the use of a combination of gabapentin or pregabalin and an antimuscarinic, preferably oxybutynin.

Both gabapentin and pregabalin are known to be effective in the treatment of pain (see D1-D4 and D9, passages cited in the international search report). Moreover, oxybutynin is also described in D9 to be used for the treatment of chronic pain of

neuropathic and nociceptive origin.

The use of combination of the two active compounds for the same medical application represents a simple juxtaposition of two known compounds using their known properties which is not considered as comprising an inventive step (Guidelines C.IV-Annex, 2.1). Such a combination can be considered as inventive in case the combination provides an unexpected beneficial effect. The application comprises no technical data showing such an unexpected synergistic effect of the combination in the treatment of pain. Therefore, the subject-matter of claims 1-33 is considered as lacking an inventive step under Art. 33(3) PCT.

4. **Industrial applicability (Art. 33(4) PCT)**

4.1 For the assessment of the present claims 1-14 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

4.2 Present claims 15-33 are susceptible of industrial application and thus do not contravene Art. 33(4) PCT.

Re Item VI
Certain documents cited

Certain published documents

Application No Patent No	Publication date *(day/month/year)*	Filing date *(day/month/year)*	Priority date *(valid claim)* *(day/month/year)*
D10: WO03/070237	28.08.2003	12.02.2003	22.02.2002
D11: WO2004/054560	01.07.2004	03.12.2003	13.12.2002

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CLAIMS

What is claimed is:

1. A method for treating pain, which comprises administering to an individual in need thereof a therapeutically effective amount of an $\alpha_2\delta$ subunit calcium channel modulator in combination with a smooth muscle modulator, wherein said smooth muscle modulator is selected from the group consisting of an antimuscarinic, a β3 adrenergic agonist, and a bradykinin receptor antagonist.

2. The method of claim 1, wherein said $\alpha_2\delta$ subunit calcium channel modulator is a GABA analog.

3. The method of claim 2, wherein said GABA analog is selected from the group consisting of:

a. gabapentin or a pharmaceutically acceptable salt, enantiomer, analog, ester, amide, prodrug, metabolite, or derivative thereof; and

b. pregabalin or a pharmaceutically acceptable salt, enantiomer, analog, ester, amide, prodrug, metabolite, or derivative thereof.

4. The method of claim 1, wherein said smooth muscle modulator is an antimuscarinic.

5. The method of claim 4, wherein said antimuscarinic is selected from the group consisting of:

a. oxybutynin or an acid, salt, enantiomer, analog, ester, amide, prodrug, active metabolite, or derivative thereof;

b. tolterodine or an acid, salt, enantiomer, analog, ester, amide, prodrug, active metabolite, or derivative thereof;

c. propiverine or an acid, salt, enantiomer, analog, ester, amide, prodrug, active metabolite, or derivative thereof; and

d. solifenacin monohydrochloride or an acid, salt, enantiomer, analog, ester, amide, prodrug, active metabolite, or derivative thereof.

Amended claims

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6. The method of claim 1, wherein said $\alpha_2\delta$ subunit calcium channel modulator is gabapentin or a pharmaceutically acceptable salt, enantiomer, analog, ester, amide, prodrug, metabolite, or derivative thereof, and wherein said antimuscarinic is oxybutynin or a pharmaceutically acceptable salt, enantiomer, analog, ester, amide, prodrug, metabolite, or derivative thereof.

7. The method of claim 1, wherein said pain is neuropathic pain, nociceptive pain, or chronic pelvic pain.

8. The method of claim 1, wherein said pain is associated with interstitial cystitis, prostatitis, prostadynia, vulvar vestibulitis, vulvodynia, functional abdominal pain disorder, functional dyspepsia, or irritable bowel disorder.

9. The method of claim 1, wherein said $\alpha_2\delta$ subunit calcium channel modulator and said smooth muscle modulator are administered orally, transmucosally, sublingually, buccally, intranasally, transurethrally, rectally, by inhalation, topically, transdermally, parenterally, intrathecally, vaginally, or perivaginally.

10. The method of claim 1, wherein at least one detrimental side effect associated with single administration of said $\alpha_2\delta$ subunit calcium channel modulator or single administration of said smooth muscle modulator is lessened.

11. The method of claim 1 wherein said $\alpha_2\delta$ subunit calcium channel modulator and said smooth muscle modulator are contained within a single pharmaceutical formulation.

12. The method of claim 1, wherein said $\alpha_2\delta$ subunit calcium channel modulator and said smooth muscle modulator are contained within separate pharmaceutical formulations.

13. The method of claim 12, wherein said $\alpha_2\delta$ subunit calcium channel modulator and said smooth muscle modulator are administered concurrently.

(ARTICLE 19)
Amended claims

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14. The method of claim 12, wherein said $\alpha_2\delta$ subunit calcium channel modulator and said smooth muscle modulator are administered sequentially.

15. A pharmaceutical composition comprising an $\alpha_2\delta$ subunit calcium channel modulator in combination with a smooth muscle modulator, wherein said smooth muscle modulator is selected from the group consisting of an antimuscarinic, a β3 adrenergic agonist, and a bradykinin receptor antagonist, and wherein said $\alpha_2\delta$ subunit calcium channel modulator and said smooth muscle modulator are in amounts sufficient to treat pain.

16. The pharmaceutical composition of claim 15, wherein said $\alpha_2\delta$ subunit calcium channel modulator is selected from the group consisting of:

a. gabapentin or a pharmaceutically acceptable salt, enantiomer, analog, ester, amide, prodrug, metabolite, or derivative thereof; and

b. pregabalin or a pharmaceutically acceptable salt, enantiomer, analog, ester, amide, prodrug, metabolite, or derivative thereof.

17. The pharmaceutical composition of claim 15, wherein said smooth muscle modulator is an antimuscarinic.

18. The pharmaceutical composition of claim 17, wherein said antimuscarinic is selected from the group consisting of:

a. oxybutynin or an acid, salt, enantiomer, analog, ester, amide, prodrug, active metabolite, or derivative thereof;

b. tolterodine or an acid, salt, enantiomer, analog, ester, amide, prodrug, active metabolite, or derivative thereof;

c. propiverine or an acid, salt, enantiomer, analog, ester, amide, prodrug, active metabolite, or derivative thereof; and

d. solifenacin monohydrochloride or an acid, salt, enantiomer, analog, ester, amide, prodrug, active metabolite, or derivative thereof.

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19. A pharmaceutical composition comprising gabapentin or a pharmaceutically acceptable salt, enantiomer, analog, ester, amide, prodrug, metabolite, or derivative thereof, in combination with oxybutynin or a pharmaceutically acceptable salt, enantiomer, analog, ester, amide, prodrug, metabolite, or derivative thereof, wherein said gabapentin and said oxybutynin are in amounts sufficient to treat pain.

20. The pharmaceutical composition of claim 19 wherein said gabapentin is present in an amount from about 50 mg to about 2400 mg, and wherein said oxybutynin is present in an amount equal to or less than about 5 mg.

21. The pharmaceutical composition of claim 20 wherein said gabapentin is in an amount of about 200 mg.

22. The pharmaceutical composition of claim 20 wherein said oxybutynin is in an amount of about 2.5 mg.

23. The pharmaceutical composition of claim 20 wherein said second component is in an amount of about 1.25 mg.

24. A pharmaceutical composition comprising pregabalin or a pharmaceutically acceptable salt, enantiomer, analog, ester, amide, prodrug, metabolite, or derivative thereof, in combination with oxybutynin or a pharmaceutically acceptable salt, enantiomer, analog, ester, amide, prodrug, metabolite, or derivative thereof, wherein said pregabalin and said oxybutynin are in amounts sufficient to treat pain.

25. A pharmaceutical composition for the treatment of pain, comprising gabapentin or a pharmaceutically acceptable salt, enantiomer, analog, ester, amide, prodrug, metabolite, or derivative thereof, in combination with oxybutynin or a pharmaceutically acceptable salt, enantiomer, analog, ester, amide, prodrug, metabolite, or derivative thereof, wherein said gabapentin and said oxybutynin are

present in a ratio from about 1:1 to about 800:1 or from about 1:1 to about 1:800, respectively, based on a fraction of their respective ED_{50} values.

26. A combination for the treatment of pain, comprising gabapentin or a pharmaceutically acceptable salt, enantiomer, analog, ester, amide, prodrug, metabolite, or derivative thereof, in combination with oxybutynin or a pharmaceutically acceptable salt, enantiomer, analog, ester, amide, prodrug, metabolite, or derivative thereof, wherein said gabapentin and said oxybutynin are in a weight/weight ratio of from 1:1 to about 800:1 or from about 1:1 to about 1:800, respectively.

27. A packaged kit for a patient to use in the treatment of pain, comprising:

a. an $\alpha_2\delta$ subunit calcium channel modulator and a smooth muscle modulator;

b. a container housing said $\alpha_2\delta$ subunit calcium channel modulator and said smooth muscle modulator; and

c. instructions for carrying out drug administration of said $\alpha_2\delta$ subunit calcium channel modulator and said smooth muscle modulator in a manner effective to treat pain;

wherein said smooth muscle modulator is selected from the group consisting of an antimuscarinic, a β3 adrenergic agonist, and a bradykinin receptor antagonist.

28. The packaged kit of claim 27 wherein said $\alpha_2\delta$ subunit calcium channel modulator is selected from the group consisting of:

a. gabapentin or a pharmaceutically acceptable salt, enantiomer, analog, ester, amide, prodrug, metabolite, or derivative thereof; and

b. pregabalin or a pharmaceutically acceptable salt, enantiomer, analog, ester, amide, prodrug, metabolite, or derivative thereof.

29. The packaged kit of claim 27 wherein said antimuscarinic is selected from the group consisting of:

a. oxybutynin or an acid, salt, enantiomer, analog, ester, amide, prodrug, active metabolite, or derivative thereof;

b. tolterodine or an acid, salt, enantiomer, analog, ester, amide, prodrug, active metabolite, or derivative thereof;

c. propiverine or an acid, salt, enantiomer, analog, ester, amide, prodrug, active metabolite, or derivative thereof; and

d. solifenacin monohydrochloride or an acid, salt, enantiomer, analog, ester, amide, prodrug, active metabolite, or derivative thereof.

30. The packaged kit of claim 27 wherein said $\alpha_2\delta$ subunit calcium channel modulator is gabapentin or a pharmaceutically acceptable salt, enantiomer, analog, ester, amide, prodrug, metabolite, or derivative thereof, and wherein said antimuscarinic is oxybutynin or a pharmaceutically acceptable salt, enantiomer, analog, ester, amide, prodrug, metabolite, or derivative thereof.

31. The packaged kit of claim 30, wherein said gabapentin and said oxybutynin are contained in a single pharmaceutical formulation.

32. The packaged kit of claim 30 wherein said gabapentin and said oxybutynin are contained in separate pharmaceutical formulations.

33. The packaged kit of claim 32 wherein said instructions include directions for carrying out drug administration of said gabapentin and said oxybutynin sequentially or concurrently.